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NARRATIVE REVIEW

Pathophysiology and clinical applications of PEEP in acute brain injury

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Abstract

Mechanical ventilation is a life-sustaining treatment needed in patients with acute brain injury to maintain airway permeability, optimize gas exchange, and prevent secondary brain damage. Positive end-expiratory pressure (PEEP), a key component of mechanical ventilation, helps prevent atelectasis, improve oxygenation, and stabilize alveolar recruitment, offering potential benefits in terms of lung protection. However, neurological tolerance of PEEP can be poor in brain-injured patients. The variability in lung and chest-wall elastance, lung recruitability, cardiac function, and fluid status, as well as the integrity of cerebral autoregulation, further complicates the recommendations for the safe range of PEEP in this patient population. This review aims to explore the physiological effects of PEEP on the brain–heart–lung interplay, focusing on the direct and indirect influences of PEEP on intracranial and cerebral perfusion pressures, as well as cerebral perfusion. We also discuss the need for individualized mechanical ventilation settings to balance the respiratory benefits of PEEP against its potential adverse effects on cerebral perfusion.

Keywords: Acute brain injury, Mechanical ventilation, Positive end-expiratory pressure, Intracranial pressure

Introduction

Following acute brain injury (ABI), preventing secondary brain injury caused by local or systemic factors is a cornerstone of care to improve long-term outcomes. Patients with ABI frequently require invasive mechanical ventilation to prevent gastric aspiration, maintain airway permeability and optimize gas exchange. This approach helps minimize secondary brain injury but increases the risk of ventilator-induced lung injury (VILI) [1, 2].

During controlled mechanical ventilation, key parameters, such as the inhaled oxygen fraction, tidal volume, driving pressure, respiratory rate, and positive end-expiratory pressure (PEEP), require careful titration [3]. Positive end-expiratory pressure prevents atelectasis, increases end-expiratory lung volume and helps reopen collapsed alveoli. Thereby, optimized PEEP improves ventilation–perfusion matching and gas exchange [4–6], and may reduce the risk of secondary brain injury. Although essential for optimizing ventilation and oxygenation, applying positive pressure to the airway into the thoracic cavity—ordinarily a negative-pressure environment—can have adverse effects on the lungs, as well as on the brain and the heart, which may worsen outcomes via increased systemic inflammation [7–9]. Positive end-expiratory pressure can impair both cerebral outflow and inflow, thereby offsetting the favorable effects on gas exchange by deleterious hemodynamic effects, potentially increasing the risk of secondary brain injuries (Fig. 1).

Despite ongoing advances, there are currently no clear guidelines for setting PEEP in patients with ABI,

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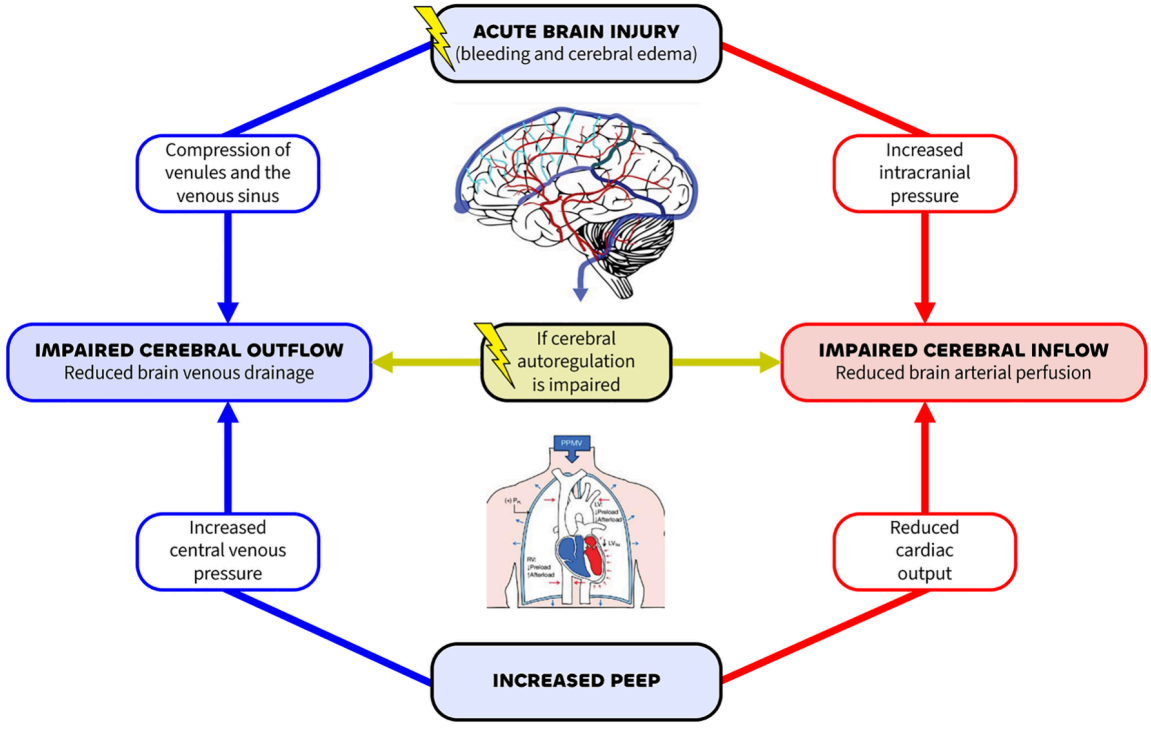

Fig. 1 Effects of acute brain injury and positive end-expiratory pressure on cerebral vascular physiology. This figure illustrates the effects of acute brain injury (**A**, **B**) and positive end-expiratory pressure (PEEP) (**C**, **D**) on cerebral arterial inflow and venous outflow. Following acute brain injury, cerebral edema and intracranial hemorrhage directly elevate intracranial pressure, resulting in **A** impaired cerebral venous drainage, particularly when accompanied by elevated central and jugular venous pressure; and **B** reduced arterial perfusion of the brain. Excessive levels of PEEP can adversely affect both left and right heart function. **C** Increased intrathoracic pressure can raise left ventricular afterload, leading to a reduction in cardiac output. **D** PEEP may impair right heart function by: (1) increasing pleural pressure, thereby elevating the transmural pressure across the right heart; and (2) increasing intrapulmonary vascular resistance due to lung overdistension, thereby raising right-ventricular afterload. Both mechanisms contribute to an elevation in central venous pressure (CVP) and, consequently, in jugular venous pressure, which may impair cerebral venous outflow. *PEEP* positive end-expiratory pressure

and whether an optimal PEEP exists for these patients remains a topic of debate [10]. The most complex scenario occurs when ABI coexists with acute respiratory distress syndrome (ARDS), which occurs in up to 25% of ABI patients [11]. In this setting, high PEEP may be required, but its application must be balanced against the risks of compromised cerebral perfusion. This review summarizes the clinical application of PEEP in patients with ABI, focusing on the complex physiological interactions between the lung, heart, and brain, with the aim of providing bedside-applicable criteria for personalized PEEP settings.

Physiological effects of peep on the respiratory system

The effects of PEEP on intrathoracic pressure

The application of PEEP increases lung volume, which, depending on the elastance of the lungs and chest wall, raises pleural pressure variability (Fig. 2). Respiratory system mechanics can be understood by examining the elastic properties of both structures: transpulmonary pressure (PL) is the difference between airway and pleural pressures, while chest-wall transmural pressure is the difference between pleural and atmospheric pressures [12]. At the end of expiration, lung and chest-wall recoil forces balance, resulting in no airflow [13, 14]. During mechanical ventilation, the interplay of airway pressure, pleural pressure, and PL depends on the relative contribution of lung and chest-wall elastance. During positive pressure ventilation, pleural and intrathoracic pressures increase proportionally to chest-wall elastance [15], but vary regionally due to the effects of gravity, mediastinal structures, and abdominal pressure. In acute respiratory distress syndrome (ARDS), which affects 10–25% of the ABI population [11, 16], lung injury is non-uniform, making respiratory mechanics and PEEP response difficult to predict. Even with low tidal volumes (< 8 ml/kg if ideal body weight), alveolar overdistension may still occur due to altered lung strain. Strain, which describes the lung

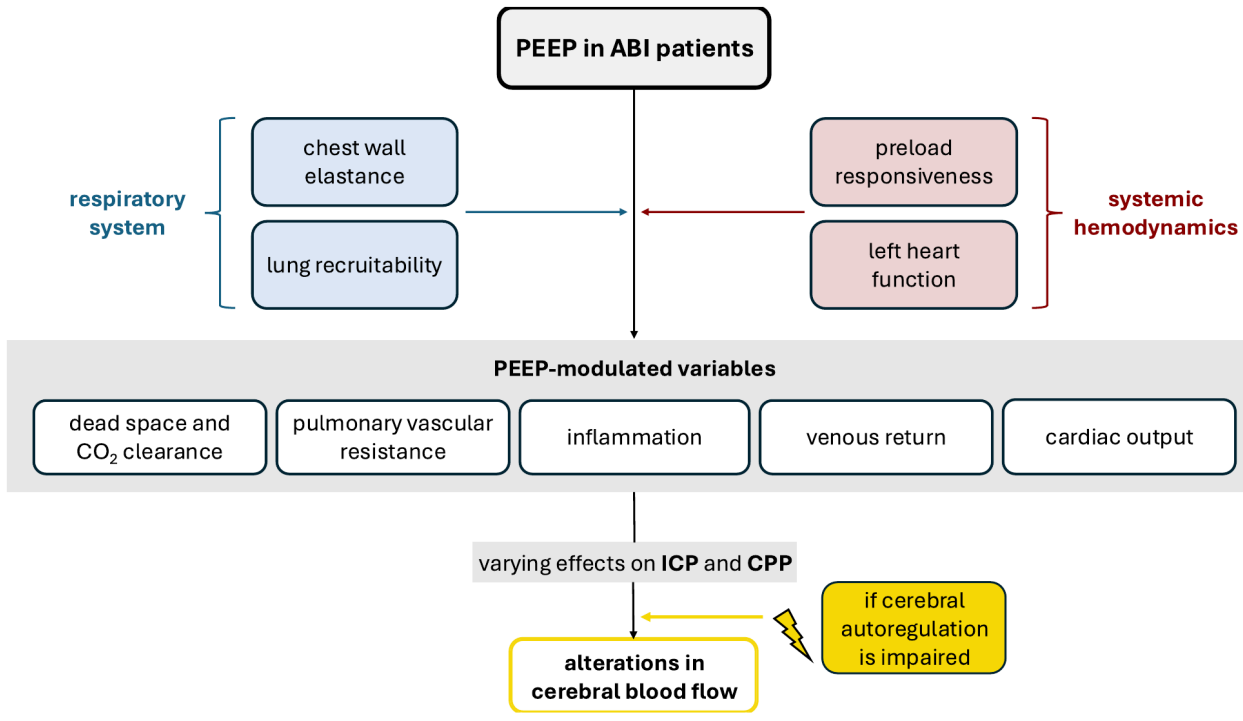

Fig. 2 PEEP-induced brain–lung and heart–lung interactions in ABI patients. *ABI* acute brain-injured, *ICP* intracranial pressure, *CPP* cerebral perfusion pressure

response to deformation, is categorized into dynamic and static components [17]. The dynamic strain reflects tidal volume-induced deformation relative to end-expiratory lung volume, while the static strain represents the PEEP-induced increase in lung volume above functional residual capacity [17–19]. PEEP may reduce dynamic strain by preventing atelectasis and increasing end-expiratory lung volume [20, 21]. However, this benefit depends on the proportion of PEEP that reopens collapsed alveoli versus further distends already open regions. While static strain always rises with PEEP, the reduction in dynamic strain varies considerably among patients [22–24]. The contribution of static versus dynamic strain to VILI remains debated and may be technique-dependent. Moreover, these are global measures that overlook regional heterogeneity, where localized stress raisers may drive injury regardless of global strain [25–27].

Experimental studies suggest that repetitive alveolar and small airway opening and closing is a major contributor to VILI, which PEEP may mitigate [28–30]. Conversely, high PEEP can also increase lung inflammation in certain patients even when combined with low tidal volume and driving pressures [31], suggesting pro-inflammatory effects that are independent of overdistension[32]. In addition, excessive PEEP levels can result in alveolar pressure exceeding the pulmonary capillary pressure, thus leading to capillary occlusion, increased dead space, and impaired CO_2 clearance [31].

Finally, excessively low PEEP can be as harmful as high levels [32]. Too little PEEP reduces functional residual capacity [29, 33], and triggers hypoxic pulmonary vasoconstriction, thereby increasing pulmonary vascular resistance and right-ventricular afterload [30, 32]. Consequently, central venous pressure may rise, potentially impairing cerebral venous return.

Physiological effects of peep on the cardiovascular system

The effects of PEEP on left heart and cardiac function

Several physiological mechanisms that protect the brain from cardiovascular-induced injuries in healthy patients are altered in patients with ABI. Impairments in cerebral autoregulation—which normally maintains constant cerebral perfusion across a wide range of systemic arterial pressures—can exacerbate cerebral hypoperfusion and increase the risk of ischemia (e.g., low cerebral perfusion pressure and intracranial pressure) during episodes of reduced cardiac output or systemic hypotension [34]. While PEEP generally has minimal hemodynamic effects in responders (those with high lung recruitability), even modest increases in PEEP have the potential

to significantly reduce preload, stroke volume, and cardiac output in non-responders, thus significantly altering brain perfusion in ABI patients with altered cerebral autoregulation [34–37]. By understanding the complex interplay between PEEP and cardiovascular function, clinicians can optimize mechanical ventilation strategies to minimize hemodynamic compromise while ensuring adequate oxygenation and ventilation (Figs. 1 and 3).

The effects of PEEP on right heart and venous return

Even though the PEEP-induced increase in intrathoracic pressure may not be uniformly transmitted to all organs and tissues [38, 39], it can significantly alter venous return dynamics because of the low-pressure gradient—typically only 4–8 mmHg—that drives venous return to the heart [40–42]. An isolated increase in central venous pressure (CVP) can, in itself, impede cerebral venous return if CVP surpasses the threshold defined by the ICP–CVP gradient [43], estimated at approximately 2.5 mm Hg in mechanically ventilated patients with 30-degree head elevation. Moreover, the collapse of cerebral venous outflow pathways, which prevents the transmission of elevated intrathoracic pressure to the intracranial compartment through the venous system in the prone position [44], is offset if PEEP increases CVP above 20 cmH_2O, thus directly transmitting the intrathoracic pressures to the brain in ABI patients [45].

The increased intrathoracic pressure caused by PEEP reduces venous return, resulting in a diminished right atrial preload and a subsequent reduction in stroke volume [39]. Furthermore, increased intrathoracic pressure reduces left ventricular afterload—the tension in the heart muscle during contraction—thereby increasing stroke volume for a given preload [46–49]. In addition, as alveoli inflate with augmented airway pressure, the compression of alveolar vessels increases right-ventricular afterload, further challenging right-ventricular function [41, 50]. Recent studies have confirmed that

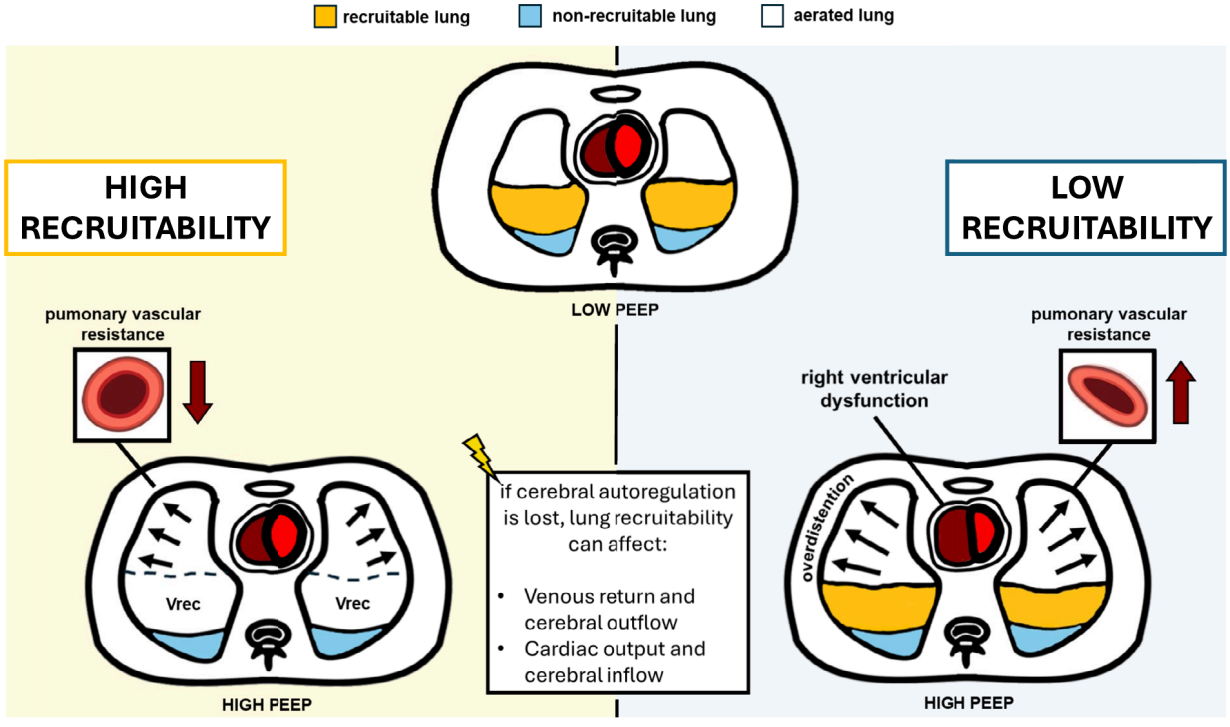

Fig. 3 Effects of PEEP in ARDS patients with high vs. low potential for lung recruitment. This image illustrates a cross section of a three-compartment lung model demonstrating how different levels of PEEP affect lung, cardiac, and cerebral physiology based on the lung's potential for recruitment. On the left, a patient with high potential for lung recruitment exhibits a marked increase in aerated lung volume due to the reopening of collapsed lung units (V_{rec}). This recruitment leads to better lung aeration, improved oxygenation and reduced pulmonary vascular resistance, contributing to better right-ventricular function. Conversely, the right panel depicts a patient with low potential for lung recruitment, where increased PEEP fails to induce meaningful reopening of collapsed units. Instead, overdistention of already open lung regions predominates, resulting in elevated pulmonary vascular resistance, right-ventricular dysfunction, reduced cardiac output, and impaired systemic oxygen delivery. This also hampers cerebral venous return. Furthermore, lung overdistention increases physiological dead space, complicating CO_2 elimination. In the presence of impaired cerebral autoregulation, these physiological changes can lead to alterations in intracranial pressure and cerebral perfusion pressure

the adverse effects of PEEP on hemodynamics are magnified in patients with low lung recruitability [30, 32], whereas they are milder and may even be positive when recruitability is high [32]. This suggests that monitoring lung recruitability, potentially with a two-step approach detailed in Figs. 4 and 5, can help personalize PEEP in ABI patients with ARDS [51, 52].

The effects of PEEP on volemic status

Sedated ABI patients on mechanical ventilation often present with relative hypovolemia and vasoplegia. Fluids and/or vasopressors raise mean systemic filling pressure, shifting the venous return curve to the right and enhancing venous return, but at the cost of increased CVP, which may impair cerebral venous outflow and worsen brain edema [53]. By decreasing venous return and increasing right-ventricular afterload, PEEP can exacerbate pre-existing hypovolemia [54]. Fluid therapy, therefore, remains a cornerstone strategy for managing PEEP-associated hemodynamic compromise. An alternative approach involves administering vasopressors to enhance vascular tone, thereby supporting venous return while minimizing the risks of positive fluid balance on brain swelling [55, 56].

The "PEEP test" has been proposed to assess fluid responsiveness in mechanically ventilated patients. In this approach, PEEP is transiently reduced to 5 cmH_2O in patients with a baseline PEEP of 10 cmH_2O or greater. Continuous monitoring of stroke volume or cardiac output allows identification of hypovolemia: an increase in cardiac index > 8.6% has a sensitivity of 96.8% (95% CI 83.3–99.9%) and specificity of 84.9% (95% CI 68.1–94.9%) for predicting fluid responsiveness [57]. This response likely reflects a decrease in right-ventricular afterload and an increase in preload resulting from the reduction in PEEP. In neuro-ICU patients, the test should be applied cautiously to avoid neurological complications, as some patients may poorly tolerate increases in PEEP [57].

Optimizing hemodynamics in ABI is crucial to improve tolerance to PEEP during prolonged mechanical ventilation. Enhancing mean systemic filling pressure with vasopressors can support venous return and mitigate the adverse cardiovascular effects of elevated PEEP.

In summary, careful titration of PEEP, guided fluid therapy, and targeted vasopressor use are essential to maintain cerebral perfusion while minimizing secondary brain injury in mechanically ventilated ABI patients.

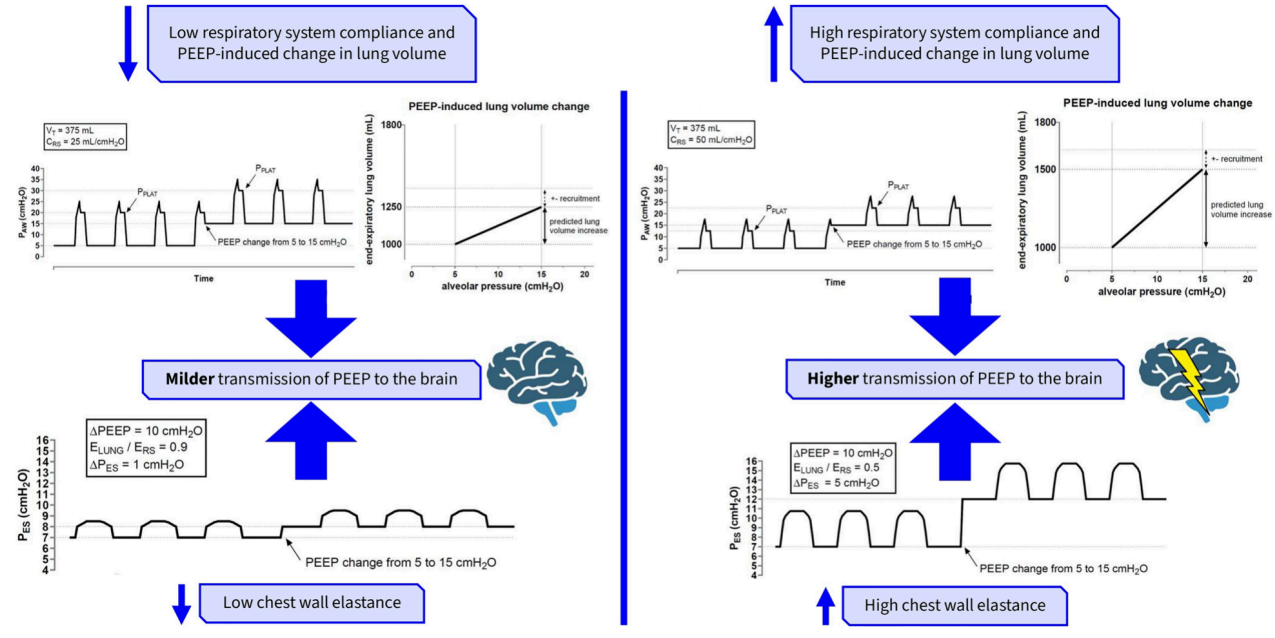

Fig. 4 Impact of respiratory mechanics on PEEP transmission to other organs. This figure illustrates how respiratory system and chest-wall elastance influence the transmission of PEEP to extrathoracic organs, including the brain. Assuming constant lung recruitment, a higher respiratory system elastance results in a smaller increase in end-expiratory lung volume in response to a given rise in PEEP as compared to when elastance is lower. Similarly, lower chest-wall elastance leads to smaller increases in pleural pressure (estimated by esophageal pressure) for the same increase in PEEP. Therefore, when lung elastance is high (low lung compliance) and chest-wall elastance is low (high chest-wall compliance), a greater proportion of the applied PEEP is absorbed within the respiratory system, minimizing its transmission to other organs, such as the heart and the brain. P_{AW} airway pressure, V_T tidal volume, P_{PLAT} plateau pressure, E_{LUNG} lung elastance, E_{RS} respiratory system elastance, C_{RE} respiratory system elastance, P_{ES} esophageal pressure

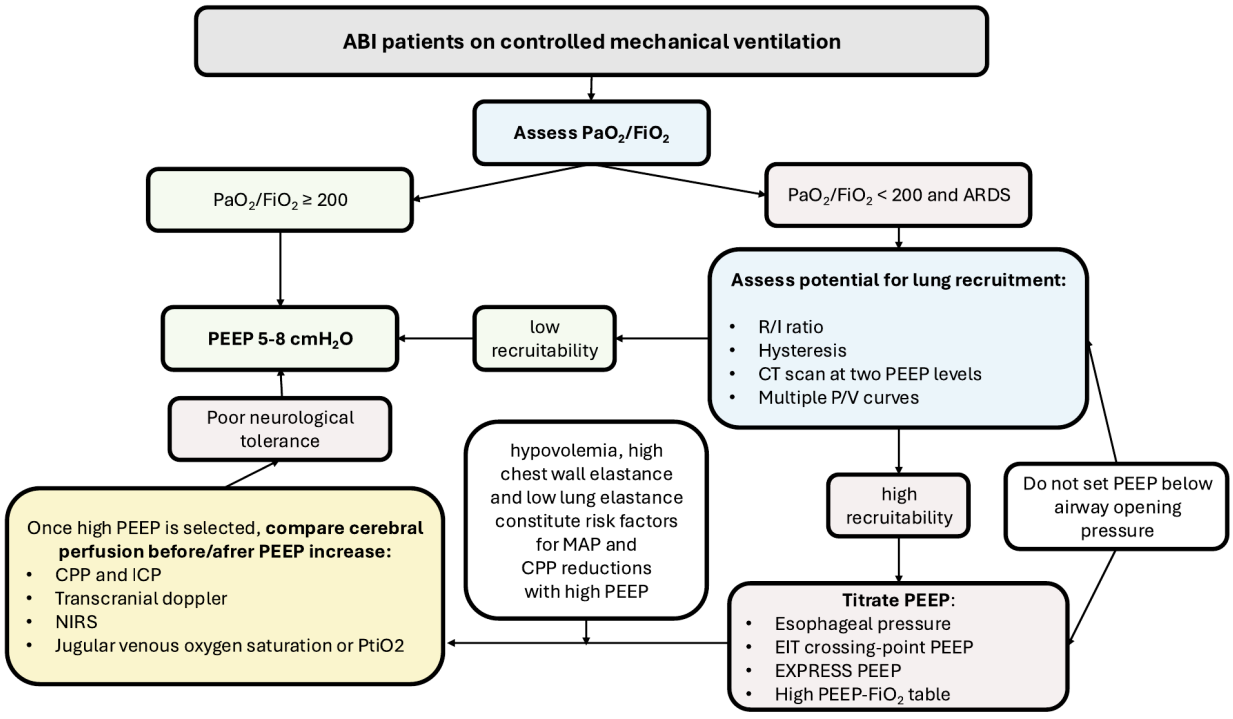

Fig. 5 Proposed algorithm for PEEP titration in ABI patients during controlled mechanical ventilation. This flowchart provides a physiologically oriented approach to setting PEEP in patients with acute brain injury (ABI). When oxygenation is not, or only mildly, impaired, low PEEP levels should be selected, as there might be no reason for the use of high PEEP. When moderate-to-severe ARDS is present together with ABI, the potential for lung recruitment should be assessed first by measuring the R/I ratio; lung hysteresis (requires dedicated ventilator software); lung CT scan at two PEEP levels; and multiple PV loops to allow the inflexion point identification. If the estimated potential for lung recruitment is small, 5–8 cm H_2O PEEP should be selected. Suppose the estimated potential for lung recruitment is high, a PEEP titration method should be applied to set PEEP precisely: such as esophageal balloon to target and end-expiratory transpulmonary pressure of 0±2, the use of electrical impedance tomography (EIT) targeting the crossing-point between lung collapse and overdistention after a PEEP trial, the EXPRESS-PEEP protocol targeting a plateau pressure of 28–30 cm H_2O, or the use of the high PEEP-FiO_2 table. Once an individualised high PEEP level is selected, brain perfusion should be reassessed to evaluate neurological tolerance. *MAP* mean arterial pressure, *CPP* cerebral perfusion pressure, *NIRS* near infrared spectroscopy; $PtiO_2$ brain tissue oxygen partial pressure, *PEEP* positive end-expiratory pressure, *ICP* intracranial pressure, *CPP* cerebral perfusion pressure

Physiological effect of peep on the brain

The interplay between the brain and lungs is often referred to as "brain–lung crosstalk". This phenomenon involves the transmission of pressures between the intrathoracic and intracranial spaces, as well as complex humoral, neural, and cellular mechanisms that influence the physiological response to interventions such as PEEP [34, 58–60].

The effects of PEEP on ICP and cerebral perfusion

From a neuroprotective perspective, the balance between the harmful and beneficial effects of PEEP mainly depends on lung recruitability and its impact on cerebral inflow (linked to cardiac output) and outflow (via venous return). This interplay is especially relevant in the early phase of ABI, when autoregulation is impaired (Fig. 3). A small physiological study in 10 patients within 72 h of ABI onset [28] examined the effects of PEEP on oxygenation and ICP. Following the application of two PEEP levels using a recruitment inflation ratio manoeuvre, higher PEEP paradoxically reduced ICP and cerebral perfusion pressure (CPP), consistent with decreased cerebral inflow rather than impaired venous outflow. Conversely, in patients with low recruitability, changes in PEEP had minimal effects on ICP, suggesting a predominant influence on venous outflow. These preliminary findings require validation in larger cohorts.

The effects of PEEP on ICP in patients with ABI have produced seemingly contradictory results. Several studies reported that increasing PEEP levels (from 5 to 15 cmH_2O) in ABI patients was associated with increased ICP, particularly in cases of poor alveolar recruitment [61, 62]. On the contrary, other studies reported no significant hemodynamic cerebral changes during PEEP increase from 0 to 12 cmH_2O in ABI patients with normal lung elastance [63, 64], probably because increased lung elastance and lower extravascular lung water minimize the transmission of PEEP to the brain [65]. Muench

et al. observed no changes in ICP or cerebral blood flow (CBF) at PEEP levels below 20 cmH_2O [66]. Moreover, consequent to the limited compliance of the cranial structure, the relationship between PEEP levels and ICP is not linear, and even small PEEP increments can influence cerebral hemodynamics. Boone et al. demonstrated that each 1 cmH_2O (0.74 mmHg) increase in PEEP resulted in a 0.31 mmHg rise in ICP (95% CI 0.07–0.54; $p=0.04$) and a 0.85 mmHg decrease in CPP (95% CI −1.48 to −0.22; $p=0.02$) [67]. Notably, focusing solely on ICP as the primary endpoint risks overlooking the broader hemodynamic consequences of PEEP. In patients with impaired cerebral autoregulation, increases in PEEP may alter brain perfusion primarily through reductions in MAP and cardiac output, which directly influence cerebral blood flow. Thus, the interpretation of ICP changes should always be integrated with a comprehensive evaluation of CPP and systemic hemodynamics, since a stable ICP can coexist with critically reduced cerebral perfusion. Conversely, a modest ICP rise may be offset by preserved MAP and adequate CPP. This underscores the importance of individualized ventilatory strategies that account not only for intracranial dynamics but also for systemic circulatory status when optimizing PEEP.

Moreover, patient responses to PEEP are heterogeneous and largely influenced by the severity of ABI—and likely alterations in cerebral autoregulation—which modulate neurological tolerance to PEEP [68]. Lung mechanics further influence the ICP response to PEEP [69]. Caricato et al. [64] demonstrated that patients with normal elastance of the respiratory system (E_{RS}) experienced greater ICP elevations and lower CPP following increased PEEP compared to those with high E_{RS}. Similarly, Mascia et al. reported that ABI patients with concomitant lung injury who were "PEEP responders"—defined by improved gas exchange and reduced lung elastance—showed no significant changes in ICP, whereas patients experiencing lung overdistension exhibited marked increases in ICP ($p<0.01$) [70]. These findings highlight that ABI patients may be categorized as responders or non-responders to PEEP, emphasizing the need for individualized ventilatory strategies.

In clinical practice, the effects of PEEP on ICP and CPP have been extensively studied, providing valuable insights for its safe use in patients with ABI. The VENTILO survey reported that PEEP levels up to 15 cmH_2O are generally applied in patients without ICH and with P/F ratios < 300. In contrast, in patients with intracranial hypertension, PEEP is often limited to 5–10 cmH_2O, reflecting concerns about potential adverse effects on intracranial dynamics [71]. Current evidence suggests that PEEP levels of 10–12 cmH_2O can be safely applied in the context of stable hemodynamics [2, 62, 72, 73], while zero PEEP should be avoided [37]. PEEP up to 15 cmH_2O may be tolerated if MAP is maintained [74], and a MAP threshold of ≥ 80 mmHg is recommended to achieve a CPP of ≥ 60 mmHg [75]. A meta-analysis including eight observational and interventional studies with 5,639 patients found no significant difference in in-hospital mortality between ABI patients receiving low versus moderate-to-high PEEP [OR 0.8 (95% CI 0.59–1.07), $p=0.13$, $I^2=80\%$] [76]. Notably, combining low tidal volume ventilation with PEEP above 6 cmH_2O improved PaO_2/FIO_2 ratios during the first 5 days of mechanical ventilation, suggesting that this strategy may help prevent respiratory complications in ABI patients. In a nationwide study including 744 patients with vascular or traumatic ABI from 20 ICUs, implementation of a standardized respiratory bundle, comprising low tidal volume (< 8 ml/kg of IBW), moderate PEEP (5–8 cmH_2O), and early extubation (within 48 h after success to spontaneous breath challenge), had limited effects on patient outcomes due to inconsistent application [76]. However, subgroup analyses and multivariate modeling indicated that compliance with this respiratory bundle was independently associated with a shorter duration of mechanical ventilation in ABI patients (risk ratio (RR) 2.25, 95% CI 1.56–3.26, $p<0.001$) [76, 77]. These findings suggest that the combination of moderate-to-high PEEP, low tidal volume ventilation, and a protocol-driven early extubation strategy may improve in-hospital outcomes in patients with ABI.

Based on the above evidence, we suggest that gradual PEEP adjustments, with increments of no more than 5 cmH_2O, rather than sudden increases, can be used to identify the "current" optimal PEEP. This is defined as the threshold that improves systemic and cerebral oxygenation without significantly affecting ICP and CPP (Fig. 5) [10]. This proposal is supported by guidelines from the European Society of Intensive Care Medicine (ESICM), which recommend applying PEEP levels similar to those used in non-brain-injured patients, and that moderate PEEP levels should be finely tuned in patients with intracranial hypertension [10]. Robba et al. [78] proposed a personalized PEEP strategy: starting with low-to-moderate PEEP in patients without lung injury and gradually increasing PEEP to improve oxygenation in those with ARDS while avoiding ICP elevation through tiered interventions (from basic, tier 0 measures to more aggressive, tier 3 strategies).

The effects of PEEP on cerebral autoregulation

Cerebral autoregulation is a critical mechanism maintaining stable CBF despite changes in intracranial volume and compliance. Preserved cerebral autoregulation allows vasoconstriction of cerebral vessels in response to

elevated ICP, stabilizing ICP and CPP, but at the potential cost of brain hypoxia [79]. In contrast, impaired cerebral autoregulation and associated brain hypoxia reduce tolerance to elevated ICP, contributing to worse outcomes [80, 81]. Consequently, the application of PEEP in patients with ABI requires careful consideration, given its complex effects on intracranial dynamics, which are mediated by cerebral autoregulation. The impact of PEEP on ICP and CPP is not uniform: patients with preserved cerebral autoregulation are more likely to tolerate moderate PEEP without adverse cerebral effects compared to patients with impaired cerebral autoregulation [64, 68–70, 78].

In the setting of impaired cerebral autoregulation, excessive PEEP may increase dead space and impair CO_2 clearance, leading to intracranial vasodilation, increased CBV, and elevated ICP, particularly in patients with reduced cerebral compliance [28, 82]. Conversely, high PEEP may also exert adverse hemodynamic effects, such as reduced MAP and cardiac output, which can paradoxically lower ICP by decreasing CBF and, consequently, cerebral blood volume [28]. Consequently, ICP changes following an increase in PEEP must be interpreted with caution and always in the context of the hemodynamic and cerebral perfusion of the individual patient.

The effects of PEEP on cerebral oxygenation

Positive end-expiratory pressure, by promoting lung recruitment, has the potential to improve cerebral and brain tissue oxygenation, even while transiently affecting cerebral blood inflow [28, 66, 83]. In healthy individuals, arterial oxygen tension (PaO_2) has a minimal influence on cerebral arterial inflow except under extreme hypoxemia ($PaO_2 < 50–60$ mmHg), a condition rarely encountered in clinical practice, where cerebral vasodilation may occur [84].

Estimating dynamic brain tissue oxygenation, using invasive methods such as brain tissue oxygen ($PtiO_2$) when available or non-invasive approaches like transcranial Doppler, is valuable to distinguish between favorable and deleterious brain responses to PEEP.

In hypoxemic traumatic brain-injured patients, increasing PEEP levels from 5 to 15 cmH_2O for at least 20 min was associated with a limited increase in $PtiO_2$ (from 27.8 ± 6.5 mmHg to 33.9 ± 6.7 mmHg) [85]. While the clinical relevance of this increase can be debated—particularly since baseline $PtiO_2$ values were above normal—it suggests that patients with brain ischemia may achieve greater oxygenation benefits from PEEP. Given the limited literature, the relationship between PEEP and cerebral oxygenation remains incompletely understood. $PtiO_2$ monitoring may provide a valuable tool to guide PEEP titration in hypoxic ABI patients, with increases in $PtiO_2$ serving as an indicator of a favorable response. Importantly, probe placement should be carefully considered, as it can affect the observed changes in brain oxygenation and interpretation of PEEP effects.

The effects of PEEP on cerebral humoral and inflammatory cascade

Acute brain injury can trigger systemic and cerebral inflammatory cascades, accompanied by a catecholamine surge. These responses promote neutrophil migration, activate alveolar macrophages, damage type II pneumocytes, increase pulmonary vascular hydrostatic pressure, and heighten capillary permeability, ultimately leading to secondary lung injury [82, 86]. Conversely, primary lung injury, as observed in ARDS, can precipitate secondary brain injury through impaired gas exchange, systemic inflammation, and microglial activation, contributing to neuronal apoptosis [87, 88]. Within this context, the application of PEEP and mechanical ventilation must be carefully tailored, integrating both respiratory and cerebral physiology to optimize oxygenation while minimizing secondary injury to either organ [89].

Future area of research

The complex interplay between the heart, brain, and lungs highlights critical knowledge gaps that warrant further investigation [90]. It is increasingly evident that static increases in airway pressure from PEEP can affect cerebral hemodynamics, with the magnitude of this effect influenced by factors, such as lung and chest-wall elastance, lung recruitability, and fluid status. While PEEP can improve gas exchange, careful attention is required due to its potential impact on cerebral inflow and outflow.

We propose that PEEP titration in patients with ABI should integrate multimodal monitoring of the brain, respiratory, and circulatory systems to balance the potential benefits and risks. However, a key unresolved question is how to manage PEEP in ABI patients when invasive neurological monitoring is unavailable. Non-invasive approaches, including transcranial Doppler or pupillometry, may be considered in moderate ABI [91], but these methods may lack the sensitivity to detect early poor tolerance to PEEP. Monitoring changes in respiratory system elastance and lung volumes during a PEEP challenge can provide valuable insights into favorable versus unfavorable cerebral responses (Fig. 4).

Conclusions

Current evidence suggests that PEEP can be safely applied in most patients with ABI when its potential cerebral effects are carefully monitored. While PEEP may increase ICP, such changes are generally negligible in patients with preserved lung elastance. Therefore,

optimal PEEP should be individualized and may evolve over time for each patient.

Multimodal neuro-monitoring—including cerebral autoregulation (e.g., Pressure Reactivity Index or transcranial Doppler) and brain oxygenation (e.g., $PtiO_2$ or microdialysis)—is essential for anticipating and managing the cerebral response to PEEP. This supports extending neuro-monitoring beyond episodes of intracranial hypertension to guide respiratory management.

In the absence of robust clinical evidence, we propose a stepwise, individualized strategy (Fig. 5): (1) treat ABI patients as at moderate-to-high risk of ARDS, always applying moderate PEEP (5–8 cmH2O) with low tidal volume to prevent lung injury; (2) adjust PEEP according to hemodynamics, respiratory mechanics, and lung morphology; (3) continuously monitor ICP, CPP, and, when available, $PtiO_2$; (4) escalate PEEP cautiously to address hypoxemia; and (5) optimize hemodynamics and correct hypovolemia to improve tolerance before considering poor neurological tolerance to increased PEEP. This approach balances pulmonary and cerebral protection, minimizing adverse effects while supporting individualized care in this vulnerable population.

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Declarations

Conflicts of interest
Dr. Roquilly receiving grants from MSD, and consulting fees from MSD. CR is a Deputy Editor for Intensive Care Medicine. She has not taken part in the review or selection process of this article. Other authors have no conflict of interest to declare.

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Abbreviations
ABI: Acute brain-injured; ARDS: Acute respiratory distress syndrome; CA: Cerebral autoregulation; CBF: Cerebral blood flow; CBV: Cerebral blood volume; CI: Interval of confidence; CPP: Cerebral perfusion pressure; C_{RE}: Respiratory system elastance; CVP: Central venous pressure; CWP: Transmural pressure across the chest wall; EIT: Electrical impedance tomography; EL: Lung elastance; ESICM: European Society of Intensive Care Medicine; ICP: Intracranial pressure; ICU: Intensive care unit; MAP: Mean arterial pressure; OR: Odds ratio; $PaCO_2$: Partial pressure of carbon dioxide; PaO_2: Arterial partial pressure of oxygen; PaO_2/FIO_2: Arterial partial pressure of oxygen to inspiratory fraction of oxygen; PEEP: Positive end-expiratory pressure; PL: Transpulmonary pressure; $PtiO_2$: Brain tissue oxygen; RR: Risk ratio; VR: Venous return; VILI: Ventilator-induced lung injury.

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